*TITLE AMENDMENTS:*

Replace the title with:

~~NEW~~ USE OF TACROLIMUS (FK506) DERIVATIVES COMBINED WITH BETA2-AGONISTS FOR THE TREATMENT OF ASTHMA

*SPECIFICATION AMENDMENTS*

Replace the paragraph beginning at page 1, line 5 with:

This invention relates to a new combination use of a FK506 ~~derivatives~~ derivative and a β2-agonist, which is useful in a medical field.

Replace the paragraph beginning at page 1, line 27 with:

FK506 derivatives, such as tacrolimus and its related compounds, are known ~~to have~~ for preventing or treating reversible obstructive airways ~~disease~~ diseases, such as asthma (USP 5,519,049). ~~And an~~ An aerosol formulation comprising FK506 derivatives ~~are~~ is also known ~~by~~ (USP 6,361,760).

Replace the paragraph beginning at page 1, line 33 with:

This invention relates to a new use of FK506 derivatives and ~~β2-agonist~~ β2-agonists for manufacturing a medicament for simultaneous, separate or sequential use for treating or preventing acute or chronic asthma.

Replace the paragraph beginning at page 1, line 36 with:

~~And further, this~~ This invention also relates to a method for treating or preventing acute or chronic asthma, by administering an effective amount of FK506 derivatives and ~~β2-agonist~~ β2-agonists, simultaneously, separately or sequentially, to a human being or an animal.

Replace the paragraph beginning at page 2, line 2 with:

A further object of this invention is to provide a composition comprising FK506 derivatives and ~~β2-agonist~~ β2-agonists as a combined preparation for treating and preventing acute or chronic asthma.

Replace the paragraph beginning at page 2, line 5 with:

~~And this~~ This invention also relates to the following~~s.~~:

Replace the paragraph beginning at page 2, line 6 with:

A use of FK506 derivatives for manufacturing a medicament for treating or preventing acute or chronic asthma with a β2-agonist, simultaneously, separately or sequentially.

Replace the paragraph beginning at page 2, line 9 with:

A composition comprising an FK506 ~~derivatives~~ derivative for treating or preventing acute or chronic asthma with β2-agonist, simultaneously, separately or sequentially.

Replace the paragraph beginning at page 2, line 11 with:

A use of a β2-agonist for manufacturing a medicament for treating or preventing acute or chronic asthma with an FK506 ~~derivatives~~ derivative, simultaneously, separately or sequentially.

Replace the paragraph beginning at page 2, line 13 with:

A composition comprising a β2-agonist for treating or preventing acute or chronic asthma with an FK506 ~~derivatives~~ derivative, simultaneously, separately or sequentially.

Replace the paragraph beginning at page 2, line 15 with:

In the present invention, the "β2-agonist" should not be limited, and should be considered to mean any ~~compounds~~ compound which can stimulate β2 receptor. Preferably, long-acting β2-agonists (such as, salmeterol, formoterol, etc) and short-acting β2-agonists (such as albuterol, bitolterol, fenoterol, isoetharine, metaproterenol, pirbuterol, terbutaline, salbutamol, etc) can be exemplified. ~~More~~ A more preferable one is a long-acting ~~β2-agonists~~ ß-2 agonist, such as, salmeterol, or formoterol.

Replace the paragraph beginning at page 2, line 21 with:

The "FK506 derivatives" means tricyclic compounds shown in EP-0184162, WO89/05303, WO93/05058, WO96/31514, and so on, the ~~disclosure~~ disclosures of which ~~is~~ are incorporated herein by reference. It is well known that those tricyclic compounds have strong immunosuppressive activity.

Replace the paragraph beginning at page 4, line 17:

Preferable protective groups in the "protected hydroxy groups" and the "protected amino" are 1-(lower alkylthio)- (lower)alkyl ~~group~~ groups such as a lower alkylthiomethyl group (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more preferably a $C_1$-$C_4$ alkylthiomethyl group, most preferably a methylthiomethyl group;

Replace the paragraph beginning at page 4, line 22:

trisubstituted silyl ~~group~~ groups such as a tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, etc.) or a lower alkyl-diarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenyl-silyl, etc.), more preferably a tri($C_1$-$C_4$)alkylsilyl group and a $C_1$-$C_4$ alkyldiphenylsilyl group, most preferably a tert-butyldimethylsilyl group and a tert-butyldiphenylsilyl group; and an acyl group such as an aliphatic, aromatic acyl group or an aliphatic acyl group substituted by an aromatic group, which are derived from a carboxylic acid, sulfonic acid or carbamic acid.

Replace the paragraph beginning at page 5, line 17 with:

Examples of the aliphatic acyl groups substituted by an aromatic group include an ar(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkoxy or trihalo(lower)alkyl, e.g., phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.

Replace the paragraph beginning at page 5, line 33 with:

$R^{24}$ is an optionally substituted ring system which may contain one or more heteroatoms, ~~Preferable~~ preferably, $R^{24}$ may be a cyclo($C_{5-7}$)alkyl group optionally having suitable substituents, and the following ones can be exemplified.

Replace the paragraph beginning at page 6, line 21 with:

The tricyclic compounds (I) and ~~its~~ their pharmaceutically acceptable ~~salt~~ salts for use in accordance with this invention are well known to have excellent immunosuppressive activity, antimicrobial activity and other pharmacological activities and, as such, ~~be~~ are of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs-host diseases, autoimmune diseases, and infectious diseases [EP-A-0184162, EP-A-0323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/04680, WO93/5059, etc.], the disclosures of which are incorporated herein by reference.

Replace the paragraph beginning at page 8, line 10 with:

The tricyclic compounds (I) may be in a form of ~~its salt~~ their salts, which ~~includes~~

include conventional non-toxic and pharmaceutically acceptable ~~salt~~salts such as the salt with inorganic or organic bases, specifically, an alkali metal salt such as sodium salt and potassium salt, an alkali earth metal salt such as calcium salt and magnesium salt, an ammonium salt and an amine salt such as triethylamine salt and N-benzyl-N-methylamine salt.

Replace the paragraph beginning at page 8, line 15:

With respect to the tricyclic compounds of the present invention, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom(s) or double bond(s), and such conformers and isomers are also included within the scope of the present invention. And further, the tricyclic ~~compounds~~compound can be in the form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Replace the paragraph beginning at page 8, line 27:

A suitable unit dose of a β2-agonist is in the range of from 0.1 μg to 500 μg, preferably from 0.5 μg to 250 μg, and more preferably between 1 μg to 100 μg. The daily dose of a β2-agonist, such as formoterol (as fumarate dihydrate), including maintenance therapy, should be in the range of from 0.1 μg to 1000 μg, preferably from 0.5 μg to 500 μg, and more preferably from 1 μg to 200 μg.

Replace the paragraph beginning at page 9, line 23:

If advisable, the β2-agonist can be mixed with the FK506 ~~derivatives~~derivative prior to its use. So, the composition comprising the said β2-agonist of the present invention may further comprise the FK506 ~~derivatives~~derivative. ~~And optionally~~Optionally, it comprises further additional active ingredients.

Replace the paragraph beginning at page 10, line 4 with:

Drugs can be given to animals placed in a plastic chamber by puffing an aerosol of the drugs. Then, an aerosolized OA solution is introduced in the chamber. Antigen-induced immediate increase in airway resistance can be monitored in a similar manner to that of Eur J Pharmacol (1996) Apr 11; 300(3):215-9.

Replace the paragraph beginning at page 12, line 20 with:

From the above invention, it is confirmed the combination use of FK506 derivatives

and ~~β2-agonist~~ β2-agonists shows a remarkable and/or synergistic prevention of asthmatic attack upon antigen exposure, relief of on-going bronchospasm, reduction of airway hyper-responsiveness and reduction of airway inflammation, which leads to better control of the condition of asthma patients. The combination use is also useful for decreasing side effects of FK506 derivatives and/or ~~β2-agonist~~ β2-agonists by providing a better control and thus by decreasing the total amount of each drug.

Replace the paragraph beginning at page 12, line 28 with:

i) An article of manufacture, comprising packaging material and an FK506 ~~derivatives~~ derivative and a β2-agonist contained within said packaging material, wherein said FK506 ~~derivatives~~ derivative and β2- agonist is therapeutically effective for treating and preventing acute or chronic asthma, and wherein said packaging material comprises a label or a written material which indicates that FK506 ~~derivatives~~ derivative and β2-agonist can be used for treating and preventing acute or chronic asthma.

Replace the paragraph beginning at page 13, line 4 with:

ii) An article of manufacture, comprising packaging material and an FK506 ~~derivatives~~ derivative and a β2-agonist contained within said packaging material, wherein said FK506 ~~derivatives~~ derivative and β2-agonist is therapeutically effective for treating and preventing acute or chronic asthma, and wherein said packaging material comprises a label or a written material which indicates that said FK506 ~~derivatives~~ derivative and β2-agonist can be used for treating and preventing acute or chronic asthma.